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Zoster Vaccine and the Risk of Postherpetic Neuralgia in Patients Who Developed Herpes Zoster Despite Having Received the Zoster Vaccine

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Abstract

Background—Although it is evident that zoster vaccination reduces postherpetic neuralgia (PHN) risk by reducing herpes zoster (HZ) occurrence, it is less clear whether the vaccine protects against PHN among patients who develop HZ despite previous vaccination.

Methods—This cohort study included immunocompetent patients with HZ. The vaccinated cohort included 1155 individuals who were vaccinated against HZ at age ≥60 years and had an HZ episode after vaccination. Vaccinated patients were matched 1:1 by sex and age with unvaccinated patients. Trained medical residents reviewed the full medical record to determine the presence of HZ-related pain at 1, 2, 3, and 6 months after HZ diagnosis. The incidence of PHN was compared between vaccinated and unvaccinated –patients.

Results—Thirty vaccinated women (4.2%) experienced PHN, compared with 75 unvaccinated women (10.4%), with an adjusted relative risk of 0.41 (95% confidence interval, .26–.64). PHN occurred in 26 vaccinated men (6.0%) versus 25 unvaccinated men (5.8%), with an adjusted relative risk of 1.06 (.58–1.94). These associations did not differ significantly by age.

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Conclusions—Among persons experiencing HZ, prior HZ vaccination is associated with a lower risk of PHN in women but not in men. This sex-related difference may reflect differences in healthcare-seeking patterns and deserve further investigation.

Keywords

herpes zoster; post-herpetic neuralgia; adult vaccination; shingles; varicella zoster virus

Postherpetic neuralgia (PHN) is one of the most common debilitating complications of herpes zoster (HZ). Although PHN has been defined in various ways, it is generally agreed that the transition from HZ to PHN occurs when pain in the area affected by HZ persists ≥3 months after crusting of the skin lesions [1,2]. PHN pain may lead to depression, fatigue, insomnia, altered activities of daily living, and decreased socialization. Individuals may also experience anorexia, physical inactivity, and difficulty concentrating [3,4]. Treatment for pain is often initiated at the time of rash onset and may be necessary for months to years. However, the effectiveness of available treatments varies [5,6]. In some patients, PHN may persist for years and can be refractory to treatment [7].

In 2006 the Advisory Committee on Immunization Practices recommended a single dose of zoster vaccine against HZ for adults aged ≥60 years (without contraindications to vaccination) for routine vaccination to prevent herpes zoster and its sequelae [8]. The Shingles Prevention Study (SPS) demonstrated that the use of the zoster vaccine reduced the burden of illness due to HZ by 61.1%, and the incidence of PHN by 66.5% [9]. A study among the Medicare population showed that the effectiveness of zoster vaccines against incidence of zoster and PHN is 48% and 59%, respectively [10]. The lower risk of PHN in the vaccinated population resulted mainly from the lower risk of HZ with vaccination.

Although it is clear that zoster vaccination is associated with a reduced risk of PHN because it reduces the occurrence of HZ, one common but unanswered question since licensure of the vaccine is whether someone who develops HZ despite being vaccinated has a lower risk of PHN than if she or he had never been vaccinated. Data from the SPS suggested some incremental benefit for the vaccine in preventing PHN among subjects who developed HZ despite vaccination. Among vaccinated SPS participants who later developed HZ, the risk of developing PHN was 8.5%, compared with 12.5% in the unvaccinated participants who developed HZ [9]. Further examination suggests that the reduced risk of developing PHN was significant only in patients aged ≥70 years (9.8% in vaccinated vs 18.5% in unvaccinated patients) [9].

Postlicensure studies offer opportunities to examine this less common outcome, which requires larger samples sizes of vaccinated patients with HZ, and to examine how vaccines perform under conditions of community use. In this cohort study, we aimed to evaluate whether patients who developed HZ despite having been vaccinated had a reduced risk of developing PHN.

METHODS

Setting

The study was conducted among members of Kaiser Permanente Southern California (KPSC), an integrated healthcare system that provides comprehensive prepaid health services for its 3.9 million members. Members are racially diverse, and >99% are community-dwelling. The demographic makeup of the KPSC membership closely mirrors that of the Southern California population [11, 12]. Compared with the racial/ethnic distribution of the United States population, the KPSC membership has twice as many individuals of Asian descent and 3 times as many Hispanics. Data regarding demographics, services, and diagnoses were tracked in KPSC electronic health records from the outpatient, emergency department, and hospital settings. Pharmacy and vaccination utilization was linked through patients' unique medical record numbers. Vaccinations received outside the health plan with appropriate documentation were also recorded.

Several factors help ensure the capture of relevant health information. HZ vaccine is provided to KPSC members at no charge, which serves as an incentive for members to receive immunizations within the system. There was also a very strong motivation for members to use services internally, because KPSC is a prepaid system. In addition, data collected during clinical care from non-KPSC providers were likely to be captured in KPSC databases because documentation of outside visits was required for reimbursement of such services by KPSC. Thus, the capture of care delivered to the members by electronic administrative data was reasonably assumed to be very comprehensive.

Study Participants

We identified a list of adults who were vaccinated against HZ at age ≥60 years after 1 January 2007 and had an episode of HZ after vaccination. Five potential unvaccinated patients with HZ were matched to each vaccinated patient with HZ for sex and date of birth (within 1 year). Diagnosis of HZ was identified from the outpatient setting by the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) codes 053.xx. An index date, the date of HZ vaccination for the vaccinated patient, was also assigned to the matched unvaccinated patients. All patients with HZ were required to have ≥1 year of continuous membership in KPSC before the index date and ≥6 months continuous membership before and after the HZ diagnosis. All patients with HZ had had no HZ diagnosis within 1 year before the index date. Because HZ vaccination is not recommended for immunocompromised patients, we excluded such patients from the study, defining them as those who had a diagnosis of human immunodeficiency virus infection, leukemia, or lymphoma or had received immunosuppressive agents within 1 year before the index date; patients who became immunocompromised after the index date were included in our analysis [13].

PHN Definition

HZ-related pain was identified as pain consistent with the HZ episode, not explained by other obvious causes (eg, rheumatoid arthritis). PHN was defined as any encounter for HZ-related pain >3 months after initial HZ diagnosis. Trained medical residents conducted

targeted reviews of the full medical record, including prescribed medications, for each participant identified from the study population to determine the presence HZ-related pain 1, 2, 3, and 6 months after HZ diagnosis, based on clinical judgment. We included the first medical encounter beyond the 6-month window to capture HZ-related pain throughout the entire 6 months.

The residents were supplied with a random sample of medical record numbers and the dates of initial HZ diagnosis of each matched set (1 vaccinated and 5 unvaccinated patients with HZ) from the study population. Reviewers were not masked as to vaccination status because this could have been noted in the medical record. The residents then reviewed the medical record of a pair including 1 vaccinated patient with HZ and 1 of the unvaccinated patients with HZ who was randomly selected from the 5. If the medical record suggested that the HZ was recurrent, if there was evidence of a positive herpes simplex virus culture or of chronic rash, or HZ was not diagnosed, then the patient was excluded. If an unvaccinated subject was excluded, the next matched subject was selected for the vaccinated subject. The residents performed the review until 1200 pairs of patients with HZ had been reached.

For each study participant, we assessed clinical characteristics related to the initial HZ episode, including the following: date of the episode, days from onset of rash to the date of visit for episode, affected dermatomes, location of rash, rash characteristics, whether or not there was a positive culture result for the varicella zoster virus, whether or not the diagnosis was made by a dermatologist or infectious disease specialist, and whether or not an antiviral prescription was given for the episode. We included information regarding the HZ episode from all medical encounters up to 30 days before and after the initial HZ date, to capture as much relevant clinical information pertaining to the HZ episode of interest as possible. For example, the date of the ICD-9-CM code that was originally identified may not have represented the first clinical visit for symptoms of the HZ episode of interest. Likewise, visits that occurred soon after the initial HZ date may have captured laboratory results that were not available on the HZ diagnosis date itself.

Data were collected on all medical encounters, including phone calls or emails (eg, to request prescriptions or refills). All medical encounters, including those that did not mention any conditions related to HZ, were reviewed and included to assess overall healthcare-seeking behavior during the 6-month period. Other covariates, such as sex, race (self-reported), healthcare utilization (defined as the number of hospitalizations or outpatient or emergency department visits within 6 months before the initial HZ diagnosis date), and chemotherapy within 6 months before the initial HZ diagnosis date were collected using electronic medical records.

Statistical Analyses

Matched pairs with HZ cases occurring within 1 month of the index date were excluded from the analysis [9]. Baseline characteristics, clinical characteristics of the HZ episode, and medical encounters in the 6 months after the HZ episode were compared between the vaccinated and the unvaccinated patients. Negative binomial models were used to estimate the relative risk (RR) and 95% confidence intervals (CI) for pain (yes/no) 90 days after the initial HZ diagnosis (defined as PHN), comparing the vaccinated and the unvaccinated

cohorts, with adjustment for age at HZ, race, calendar year of HZ diagnosis, antiviral or corticosteroid prescription at initial HZ diagnosis, visit for HZ within 3 days of rash onset, and receipt of chemotherapy and healthcare utilization (outpatient visits, emergency department visits, and hospitalizations) in the 6 months before HZ diagnosis. Age- and sex-specific RRs were also estimated, adjusted for the other variables mentioned above. SAS Enterprise Guide software (version 4.2; SAS Institute) was used for all analyses.

The protocol was reviewed and approved by the KPSC Institutional Review Board. The requirement for informed consent was waived because there was no patient contact.

RESULTS

Of the 1200 matched pairs of patients with HZ, 45 pairs were excluded because HZ occurred within 1 month of the index date, leaving 1155 pairs of patients with HZ for analysis. The distribution of baseline characteristics of the patients with HZ by vaccination status is presented in Table 1. About two-thirds (62.6%) of the study participants were female. The age distribution was comparable between groups; about 60% of the patients with HZ were aged ≥70 years at the index date. The distribution of race differed between the vaccinated and unvaccinated cohorts (69.7% white in the vaccinated vs 49.3% white in the unvaccinated). The number of outpatient visits during the 6 months before the first visit for HZ was higher for the vaccinated than for the unvaccinated cohort (mean, 4.1 vs 3.5 visits), but the number of emergency department visits and hospitalizations showed no difference. For the vaccinated cohort, the mean period of time from vaccination to first visit for HZ was 692.5 days, compared with 471.8 days for the unvaccinated cohort.

Table 2 presents the clinical characteristics and treatment of the initial HZ episode by vaccination status. Approximately 50% of patients were seen for their HZ rash within 3 days of rash onset, and this did not vary by vaccination status or sex. More than 80% of the medical records lacked information on dermatome. The vaccinated group had a smaller proportion of patients with rash on the chest. Close to 90% of the records indicated that patient's rash was unilateral, with the remaining records not describing laterality. More than two-thirds of the records described the rash as vesicular, and this description was more common in the unvaccinated patients (73.3% vs 67.7%). Most patients were prescribed antiviral treatment. Treatment was slightly more common in the unvaccinated patients and did not vary by sex. The HZ diagnosis was uncertain more frequently in vaccinated than in unvaccinated patients with HZ.

Table 3 reports the medical encounters during the 6-month period after the initial HZ visit. The vaccinated patients had a mean of 8.5 encounters, versus 7.7 in the unvaccinated patients. The vaccinated cohort had fewer encounters for HZ-related pain than the unvaccinated group (mean, 0.8 vs 1.2, excluding the initial visit for HZ; $P < .01$). Furthermore, for women the mean number of visits was 1.3 for unvaccinated and 0.8 for vaccinated patients. In contrast, for men the mean number was 0.8 for unvaccinated and 1.0 for vaccinated patients. Unvaccinated men had significantly fewer visits than unvaccinated women (mean, 0.8 vs 1.3; $P < .05$).

Table 4 presents HZ-related pain in the 6 months after HZ diagnosis by sex and by vaccination status. In men, 47 (10.9%) of the vaccinated patients had visits for HZ-related pain occurring >1 month after the initial visit, compared with 65 (15.0%) of the unvaccinated patients. The proportions of vaccinated versus unvaccinated men with visits mentioning HZ-related pain more than 2, 3, and 6 months after the initial HZ diagnosis were 8.6% versus 9.0%, 6.0% versus 5.8%, and 3.0% versus 2.3%, respectively; the RRs for vaccinated versus un-vaccinated men at 1, 2, 3, and 6 months were 0.7, 0.9, 1.0, and 1.3 (*P* for trend, .06). In contrast, the proportions of vaccinated versus unvaccinated women with visits mentioning HZ-related pain at more than 1, 2, 3, and 6 months after the initial HZ diagnosis were 12.9% versus 21.6%, 6.2% versus 14.5%, 4.1% versus 10.4%, and 1.0% versus 4.6% (RR, 0.6, 0.4, 0.4, and 0.2; *P* for trend, <.01). At 3 months after HZ diagnosis, men were significantly less likely than women to have PHN in the unvaccinated group (5.8% vs 10.4%; $P < .05$) but nonsignificantly more likely to have PHN in the vaccinated group (6.0% vs 4.1%; $P > .05$). The same direction of findings was true at 6 months, statistically significant in both groups (unvaccinated, 2.3% in men vs 4.6% in women; vaccinated, 3.0% vs 1.0%).

Table 5 presents the RR for PHN (HZ-related pain lasting 3 months after the initial HZ diagnosis) in vaccinated versus un-vaccinated cohorts. Overall, vaccinated subjects had about 60% of the risk compared with unvaccinated patients (adjusted RR, 0.59; 95% CI, .41–.85). However, sex-specific analysis revealed that the risk was mainly reduced in women (adjusted RR, 0.41 [95% CI, .26–.64] in women and 1.06 [.58–1.94] in men). The reduced risks in women were comparable in the 60–69- and ≥70-year age groups (RR, 0.30 [95% CI, .12–.74] and 0.40 [.25–.64], respectively). Finally, the RR estimates remained unchanged when the patients with uncertain HZ diagnosis were excluded from the analysis.

DISCUSSION

The SPS has demonstrated that zoster vaccine reduces the risk of PHN among the vaccinated by reducing HZ occurrence [9]. It also demonstrated that zoster vaccine reduced the risk of PHN among vaccinated persons who developed HZ, particularly in vaccine recipients aged ≥70 years. Our study confirms the findings in a more broadly representative population and suggests that HZ vaccination provides incremental benefits beyond simply reducing HZ incidence.

Based on medical encounters for HZ-related pain occurring ≥3 months after the initial HZ visit to define PHN, our results suggest that female patients who develop HZ despite vaccination had a lower risk of PHN than unvaccinated female patients with HZ. We found this benefit in both 60–69- and ≥70-year age groups. The vaccine seems most effective in preventing the most prolonged episodes of PHN, confirming the results noted in the SPS. Comparing vaccinated and unvaccinated female patients, the reductions in the RR of HZ-related pain were greater for HZ-related pain of longer duration (RR, 0.6, 0.4, 0.4, and 0.2 for pain at 1, 2, 3, and 6 months, respectively). This finding is clinically important because patients and providers may be more likely to consider vaccination if it can prevent the most prolonged episodes of PHN. The data suggest that the pathways by which HZ vaccination interferes with development of HZ (ie, boosted cell-mediated immunity), though not

sufficient to prevent all HZ, may reduce the severity and duration of the HZ episodes that do occur.

We did not observe a reduced risk of PHN associated with vaccination among men in any age group. This striking sex-specific difference could be random error because of the small number of PHN cases, caused by an unrecognized biological phenomenon, or related to differential healthcare-seeking behavior by sex. Almost all patients seek medical care for acute HZ, regardless of sex [14, 15]. Patients may be particularly concerned about the symptoms of this condition with its acute onset of unilateral pain and dysesthesias. If they do recognize the symptoms of HZ, they may also realize that the condition needs to be promptly treated. Electronic health data regarding medically attended HZ may therefore represent a sensitive proxy for actual HZ [14], particularly in a medical setting such as KPSC, with its prepaid healthcare and easy access.

On the other hand, if pain persists and PHN develops, healthcare-seeking behavior may change, particularly because treatments for PHN pain are often inadequately effective and associated with adverse effects. As patients become aware of the source of the pain over time, many may not bother with clinic appointments or medication refills. Healthcare-seeking behavior might become more variable, resulting in opportunities for confounding (ie, when vaccination and healthcare-seeking behaviors are correlated). There is, for instance, substantial documentation that among patients with chronic pain, women are more likely to seek medical care and request medications [16–19]. Indeed, among unvaccinated patients in our study, men had fewer visits for PHN (≥3 months of HZ-related pain) than women (5.8% vs 10.4%), whereas for unvaccinated subjects in the SPS, which used active surveillance to inquire about subjects' pain, men were more likely than women to report HZ-related pain after 3 months (14.1% vs 10.3%) [9].

Furthermore, in one of our ongoing studies where HZ-related pain is identified by interviewing patients using the Zoster Brief Pain Inventory, as in the SPS, the incidences of HZ-related pain in unvaccinated men were 31.8%, 20.7%, and 13.9% at 1, 2, and 3 months after HZ diagnosis. The incidence of PHN defined by medical encounter among unvaccinated men in the current study (5.8%) is significantly lower than that defined by inquiry (13.9%). This difference is less pronounced in unvaccinated women (10.4% vs 11.4% for PHN incidence defined by encounter vs inquiry [20]).

Defining PHN using healthcare encounters as evidence of pain, rather than using self-reported HZ pain, could underestimate the incidence of PHN and potentially introduce confounding if vaccinated and unvaccinated individuals have different healthcare-seeking behavior for chronic pain. One should be cautious about comparing findings from studies using medically attended PHN (ie, using electronic medical records) as the end point with findings from studies using self-reported PHN because different methods for PHN ascertainment could lead to different estimates of PHN incidence and vaccine effectiveness for preventing PHN. Further studies comparing self-reported HZ pain with healthcare seeking by sex, vaccination status, and other factors would help elucidate potential confounders. If the sex-specific results are due to a true biological phenomenon (ie, differential HZ-vaccine immunogenicity), this would have implications in terms of basic

biology and vaccine policy. From a healthcare utilization perspective, our results show that when HZ occurs those who have been vaccinated with the zoster vaccine have fewer visits for HZ-related pain, at least among women.

Some potential limitations deserve mentioning. Although we made efforts to correctly identify incident HZ in vaccinated and unvaccinated groups by excluding cases of recurrent HZ, herpes simplex, or other chronic rashes, some misclassification may have occurred. In another study, we found that 85% of clinically diagnosed cases were confirmed as HZ by polymerase chain reaction testing [21]. We were also unable to assess severity of pain because it was not consistently recorded in the medical record. Furthermore, the documentation of pain or discomfort in the record was sometimes not clear; in these instances, the physicians reviewing the records had to make subjective determinations. In addition, although residents were instructed not to look for vaccination history, it was documented in the records and some reviews may have been unmasked as to vaccination status. Finally, patients with more healthcare encounters were more likely to have evidence of HZ-related pain. This pattern could bias the estimate of association toward the null because vaccinated individuals tended to visit physicians more frequently.

In conclusion, we provide evidence that HZ vaccination yields benefits beyond simple prevention of HZ. Furthermore, the vaccine is most effective at preventing the most prolonged episodes of PHN. Although uptake of HZ vaccine was low after introduction of the vaccine, rates have more recently started to increase. Ideally, as physicians and patients recognize the full benefits of HZ vaccination, more persons will take advantage of the vaccine to decrease the risk of long-term pain and potential disability.

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Table 1

Baseline Characteristics of HZ Cohort by Vaccination Status

Characteristic	Patients, No. (%)[a]		*P* Value
	Unvaccinated HZ Cohort (n =1155)	Vaccinated HZ Cohort (n =1155)	
Age			.15
60–69 y	489 (42.3)	455 (39.4)	
≥70 y	666 (57.7)	700 (60.6)	
Mean (SD), y	71.6 (6.9)	72.2 (7.0)	
Sex			>.99
Male	432 (37.4)	432 (37.4)	
Female	723 (62.6)	723 (62.6)	
Race			<.01
White	569 (49.3)	805 (69.7)	
Black	169 (14.6)	47 (4.1)	
Asian/Pacific Islander	99 (8.6)	117 (10.1)	
Hispanic	286 (24.8)	155 (13.4)	
Other/multiple	14 (1.2)	11 (1.0)	
Unknown	18 (1.6)	20 (1.7)	
Outpatient visits in 6 mo before 1st visit for HZ			<.01
0	184 (15.9)	98 (8.5)	
1–4	653 (56.5)	636 (55.1)	
5–10	259 (22.4)	359 (31.1)	
≥11	59 (5.1)	62 (5.4)	
Mean No. (SD)	3.5 (3.5)	4.1 (3.4)	
Median No. (IQR)	2 (1.0–5.0)	3 (2.0–6.0)	
ED visits in 6 mo before 1st visit for HZ			.24
0	950 (82.3)	964 (83.5)	
1	143 (12.4)	146 (12.6)	
≥2	62 (5.4)	45 (3.9)	
Mean No. (SD)	0.3 (0.9)	0.2 (0.6)	
Median No. (IQR)	0 (0.0–0.0)	0 (0.0–0.0)	
Hospitalizations in 6 mo before 1st visit for HZ			.83
0	1048 (90.7)	1056 (91.4)	
1	80 (6.9)	73 (6.3)	
≥2	27 (2.3)	26 (2.3)	
Mean No. (SD)	0.1 (0.5)	0.1 (0.5)	
Median No. (IQR)	0 (0.0–0.0)	0 (0.0–0.0)	
Chemotherapy received in 6 mo before 1st visit for HZ			.27
Yes	13 (1.1)	8 (0.7)	

Characteristic	Patients, No. (%)[a]		*P* Value
	Unvaccinated HZ Cohort (n =1155)	Vaccinated HZ Cohort (n =1155)	
No	1142 (98.9)	1147 (99.3)	
Time from index date to 1st visit for HZ			<.01
<180 d	335 (29.0)	89 (7.7)	
180 d–1 y	224 (19.4)	183 (15.8)	
>1 y–2 y	326 (28.2)	369 (31.9)	
>2 y	270 (23.4)	514 (44.5)	
Mean duration (SD), d	471.8 (384.2)	692.5 (375.1)	
Median duration (IQR), d	378 (155–711)	666 (383–996)	

Abbreviations: ED, emergency department; HZ, herpes zoster; IQR, interquartile range; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

Table 2

Clinical Characteristics and Antiviral and Corticosteroid Treatment of HZ Cohort by Vaccination Status

Characteristics and Treatment	Patients, No. (%)[a]		*P* Value
	Unvaccinated HZ Cohort (n =1155)	Vaccinated HZ Cohort (n = 1155)	
Time from rash onset to initial HZ diagnosis			.16
0 d	114 (9.9)	107 (9.3)	
1–3 d	473 (41.0)	444 (38.4)	
4–6 d	228 (19.7)	215 (18.6)	
>6 d	242 (21)	295 (25.5)	
Data missing	98 (8.5)	94 (8.1)	
Mean time (SD), d	4.6 (6.9)	5.1 (8.6)	
Median time (IQR), d	3 (2.0–6.0)	3 (2.0–7.0)	
Dermatomal distribution[b]			.20
Single C/multiple C	35 (3.0)	30 (2.6)	
Single T/multiple T	132 (11.4)	114 (9.9)	
Single L/multiple L	36 (3.1)	24 (2.1)	
Single S/multiple S	14 (1.2)	7 (0.6)	
Multiple dermatomes	7 (0.6)	7 (0.6)	
Unknown	931 (80.6)	973 (84.2)	
Location of rash			
Abdomen	219 (19.0)	216 (18.7)	.87
Back	465 (40.3)	442 (38.3)	.33
Chest	284 (24.6)	229 (19.8)	.01
Head or neck	254 (22.0)	290 (25.1)	.08
Arm or hand (left or right)	131 (11.3)	131 (11.3)	1.00
Leg or foot (left or right)	125 (10.8)	115 (10.0)	.50
Pelvis or buttocks	92 (8.0)	97 (8.4)	.70
Unknown	23 (2.0)	24 (2.1)	.88
Unilateral rash			.49
Yes	999 (86.5)	1018 (88.1)	
No	35 (3.0)	30 (2.6)	
Unknown	121 (10.5)	107 (9.3)	
Linear/dermatomal rash			.38
Yes	523 (45.3)	492 (42.6)	
No	25 (2.2)	30 (2.6)	
Unknown	607 (52.6)	633 (54.8)	
Vesicular rash			.01
Yes	847 (73.3)	782 (67.7)	
No	84 (7.3)	93 (8.1)	

Characteristics and Treatment	Patients, No. (%)[a]		*P* Value
	Unvaccinated HZ Cohort (n =1155)	Vaccinated HZ Cohort (n = 1155)	
Unknown	224 (19.4)	280 (24.2)	
Maculopapular or crusted rash			.90
Yes	367 (31.8)	376 (32.6)	
No	108 (9.4)	110 (9.5)	
Unknown	680 (58.9)	669 (57.9)	
Diagnosed by dermatologist or infectious disease specialist			.03
Yes	24 (2.1)	37 (3.2)	
No	1123 (97.2)	1100 (95.2)	
Unknown	8 (0.7)	18 (1.6)	
Positive culture for varicella zoster virus			.27
Yes	38 (3.3)	40 (3.5)	
No	1117 (96.7)	1112 (96.3)	
Unknown	0 (0.0)	3 (0.3)	
Antiviral prescription			.01
Yes	1035 (89.6)	995 (86.1)	
No	120 (10.4)	160 (13.9)	
Corticosteroid prescription			.78
Yes	201(17.4)	206 (17.8)	
No	954 (82.6)	949 (82.2)	
Evidence of uncertain HZ diagnosis			.01
Yes	49 (4.2)	77 (6.7)	
No	1106 (95.8)	(93.3)	

Abbreviations: HZ, herpes zoster; IQR, interquartile range; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]C = Cervical, T =Thoracic, L = Lumbar, S = Sacral.

Table 3

Medical Encounters in the 6 Months After HZ Diagnosis by Vaccination Status

Medical Encounters	Patients, No. (%)[a]		*P* Value
	Unvaccinated HZ Cohort (n= 1155)	Vaccinated HZ Cohort (n =1155)	
Total medical encounters in 6 mo after HZ diagnosis (including 1st visit)			.10
1	72 (6.2)	56 (4.8)	
2–8	728 (63)	689 (59.7)	
9–15	235 (20.3)	260 (22.5)	
16–22	76 (6.6)	95 (8.2)	
>22	44 (3.8)	55 (4.8)	
Mean No. (SD)	7.7 (6.4)	8.5 (7.3)	
Median No. (IQR)	6 (3.0–10.0)	6 (4.0–11.0)	
Total encounters for HZ-related pain in 6 mo after HZ diagnosis (excluding 1st visit)			<.01
0	611 (52.9)	705 (61.0)	
1–2	367 (31.8)	345 (29.9)	
3–4	111 (9.6)	64 (5.5)	
5–8	46 (4)	32 (2.8)	
>8	20 (1.7)	9 (0.8)	
Mean No. (SD)	1.2 (2.1)	0.8 (1.6)	
Median No. (IQR)	0 (0.0–2.0)	0 (0.0–1.0)	
Outpatient/email/phone encounters for HZ-related pain in 6 mo after HZ diagnosis (excluding 1st visit)			<.01
0	620 (53.7)	708 (61.3)	
1–4	472 (40.9)	411 (35.6)	
5–8	45 (3.9)	28 (2.4)	
>8	18 (1.6)	8 (0.7)	
Mean No. (SD)	1.1 (2.0)	0.8 (1.6)	
Median No. (IQR)	0 (0.0–1.0)	0 (0.0–1.0)	
ED visits for HZ-related pain in 6 mo after HZ diagnosis (excluding 1st visit)			.07
0	1118 (96.8)	1135 (98.3)	
1	31 (2.7)	17 (1.5)	
>1	6 (0.5)	3 (0.3)	
Mean No. (SD)	0.0 (0.2)	0.0 (0.1)	
Median No. (IQR)	0 (0.0–0.0)	0 (0.0–0.0)	
Hospitalizations for HZ-related pain in 6 mo after HZ diagnosis (excluding 1st visit)			.12
0	1147 (99.3)	1153 (99.8)	
1	5 (0.4)	2 (0.2)	
>1	3 (0.3)	0 (0)	

Medical Encounters	Patients, No. (%)[a]		*P* Value
	Unvaccinated HZ Cohort (n= 1155)	Vaccinated HZ Cohort (n =1155)	
Mean No. (SD)	0.0 (0.1)	0.0 (0.0)	
Median No. (IQR)	0 (0.0–0.0)	0 (0.0–0.0)	

Abbreviations: ED, emergency department; HZ, herpes zoster; IQR, interquartile range; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

Table 4

HZ-Related Pain in the 6 Months After HZ Diagnosis by Sex and by Vaccination Status

Timing of HZ-Related Pain by Sex	Patients, No. (%)		RR[a] (95% CI)	*P* Value
	Unvaccinated HZ Cohort (Male n= 432; Female n= 723)	Vaccinated HZ Cohort (Male n =432; Female n =723)		
Lasting 1 mo after initial diagnosis				
Male patients	65 (15.0)	47 (10.9)	0.7 (.5–1.1)	.07
Female patients	156 (21.6)	93 (12.9)	0.6 (.5–.8)	<.01
Lasting 2 mo after initial diagnosis				
Male patients	39 (9.0)	37 (8.6)	0.9 (.6–1.5)	.81
Female patients	105 (14.5)	45 (6.2)	0.4 (.3–.6)	<.01
Lasting 3 mo after initial diagnosis				
Male patients	25 (5.8)	26 (6.0)	1.0 (.6–1.8)	.89
Female patients	75 (10.4)	30 (4.1)	0.4 (.3–.6)	<.01
Lasting 6 mo after initial diagnosis				
Male patients	10 (2.3)	13 (3.0)	1.3 (.6–3.0)	.53
Female patients	33 (4.6)	7 (1.0)	0.2 (.1–.5)	<.01

Abbreviations: CI, confidence interval; HZ, herpes zoster; RR, relative risk.

[a]The *P* value for trend of RR was .06 in male and <.01 in female patients.

Table 5

RR and 95% CI Estimates for Association between HZ Vaccination and PHN

Age Group by Sex	Vaccination Group	Patients With PHN, No. (%)	Unadjusted RR (95% CI)	Adjusted RR[a] (95% CI)
Male patients by age, y				
60–69	Unvaccinated	8 (4.62)	1.00	1.00
	Vaccinated	8 (4.94)	1.07 (.40–2.85)	1.16 (.36–3.73)
≥70	Unvaccinated	17 (6.56)	1.00	1.00
	Vaccinated	18 (6.67)	1.02 (.52–1.97)	0.93 (.44–1.94)
Total	Unvaccinated	25 (5.79)	1.00	1.00
	Vaccinated	26 (6.02)	1.04 (.60–1.8)	1.06 (.58–1.94)
Female patients by age, y				
60–69	Unvaccinated	27 (8.54)	1.00	1.00
	Vaccinated	7 (2.39)	0.28 (.12–.64)	0.30 (.12–.74)
≥70	Unvaccinated	48 (11.79)	1.00	1.00
	Vaccinated	23 (5.35)	0.45 (.28–.75)	0.40 (.25–.64)
Total	Unvaccinated	75 (10.37)	1.00	1.00
	Vaccinated	30 (4.15)	0.40 (.26–.61)	0.41 (.26–.64)
All patients by age, y				
60–69	Unvaccinated	35 (7.16)	1.00	1.00
	Vaccinated	15 (3.30)	0.46 (.25–.84)	0.53 (.27–1.02)
≥70	Unvaccinated	65 (9.76)	1.00	1.00
	Vaccinated	41 (5.86)	0.60 (.41–.89)	0.63 (.41–.96)
Total	Unvaccinated	100 (8.66)	1.00	1.00
	Vaccinated	56 (4.85)	0.56 (.40–.78)	0.59 (.41–.85)

Abbreviations: CI, confidence interval; HZ, herpes zoster; PHN, postherpetic neuralgia; RR, relative risk.

[a]Estimates were adjusted for age at HZ, race, calendar year of HZ diagnosis, antiviral prescription, corticosteroid prescription, visit for HZ within 3 days of rash onset, and receipt of chemotherapy or healthcare utilization (outpatient visits, emergency department visits, and hospitalizations) in the 6 months before HZ diagnosis.